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Infants of mothers with a high and of mothers with a low insulin response to glucose infusion. Glucose tolerance, insulin response and clinical appearance during the early neonatal period

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Diabetes mellitus in a pregnant woman affects the development of the fetal pancreas [2] resulting in hyperinsulinism of the newborn infant who also often presents typical clinical traits [8, 23, 32]. Furthermore, diabetic women may produce large-for-date infants long before their disturbed carbohydrate metabolism is diagnosed [13, 17]. It is not known, however, at which stage in the development of diabetes this effect on the fetus appears.

CERASI and LUFT [4, 5] have defined **"prediabetes"** as a **stage in which there is a normal glucose tolerance but a decreased insulin response to glucose infusion** (GIT). In a previous study [6] it was demonstrated that in a group of low insulin responders — in which the prediabetic individuals can be expected to be found — the glucose tolerance remained normal throughout pregnancy, while the insulin response increased gradually. The glucose tolerance and insulin response to an intravenous glucose load (IVGTT) of the infants borne by these women and by the control group of high responders were studied. These results together with clinical data on the infants and their mothers are presented here.

1 Material and methods

The groups consisted of 14 infants of mothers with a high initial insulin response to glucose (IHR) and 13 infants of mothers with a low response (ILR). Basic clinical data are presented in Tab. I.

Before the study consent was obtained from the parents.

1.1 Mothers

The classification of the mothers into high and low responders was made on the basis of their initial insulin response in the non-pregnant state to a continuous glucose infusion (GIT) according to the technique and criteria described by CERASI and LUFT [4].

Curriculum vitae

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Tab. I. Clinical data on 27 newborn healthy infants. 22 of them underwent an intravenous glucose tolerance test at 4—24 hours age. M = male, F = female.

No	Sex	Gestational age (weeks)	Birth weight (g)	Length (cm)	Weight loss (per cent)	Age at IVGTT (hrs)	k-value at IVGTT
Infants of **high** insulin responders (IHR)							
1	M	38	2560	49	9.8	12	0.77
2	M	41	3230	49	5.5	10	1.13
3	F	40	3240	50	5.9	15	0.87
4	F	40	4230	54	6.1	22	2.10
5	F	41	4420	52	4.5	22	1.27
6	M	40	3860	53	3.1	5	0.76
7	F	40	4150	52	10.1	—	—
8	M	41	3380	51	5.0	16	1.69
9	F	40	3320	50	5.4	—	—
10	M	41	4470	53	4.7	20	1.16
11	F	41	3450	50	5.7	—	—
12	F	41	4410	53	5.0	16	0.55
13	F	41	3600	51	6.1	10	1.05
14	F	41	3030	49	5.3	23	0.83
$\bar{x}$		40.4	3668	51.1	5.9	15.5	1.11
SD		0.9	596	1.7	1.9	5.9	0.45
Infants of **low** insulin responders (ILR)							
21	M	41	3600	51	6.3	—	—
22	F	40	3090	49	6.1	4	1.52
23	M	38	3270	49	7.4	21	1.01
24a	M	41	3740	52	8.8	—	—
24b	M	39	3410	49	8.3	6	1.87
25	F	40	3110	49	4.5	11	1.28
26	M	43	3720	52	4.8	19	0.44
27a	M	41	3450	50	7.2	5	2.10
27b	F	40	3480	49	9.5	23	1.55
28	M	40	3530	52	6.3	10	1.01
29	F	41	3900	52	9.2	15	2.72
30	F	40	3240	49	5.6	11	1.08
31	M	42	3700	53	7.0	14	0.83
$\bar{x}$		40.5	3477	50.5	7.0	12.6	1.40
SD		1.3	252	1.6	1.6	6.4	0.64

The high responders were slightly, but not significantly, older than the low responders (29.2 ± 3.5 years as compared to 26.8 ± 3.0 years). Their mean weight before pregnancy was 60.1 ± 9.2 kg ($\bar{x} \pm$ SD) as compared to 52.7 ± 5.7 kg for the low responders ($p > 0.05$) and the mean body height 168.8 ± 5.2 cm and 165.0 ± 5.6 cm, respectively ($p > 0.05$). Their urinary estriol excretion was followed weekly during the latter half of the pregnancy and the blood levels of chorionic somatomammotropin (HCS) were determined at approximately 22 and 36 weeks pregnancy in 20 women.

1.2 Infants

a) **At delivery.** Immediately at birth the cord was clamped in 9 IHR and 9 ILR and umbilical venous blood was drawn to determine glucose and insulin. In 5 IHR and 7 ILR plasma glucose was also determined in umbilical arterial blood at birth and in femoral vein blood at 20, 40, 60 and 120 min age.

b) **IVGTT.** In 11 IHR and 11 ILR an IVGTT was performed 4—24 hours after birth (Tab. I). The lower time limit was chosen to avoid the first intense period of metabolic adaptation after birth. The upper time limit was set at 24 hours,

since after this time the difference in k-value at IVGTT between infants of diabetic mothers and those of healthy mothers has been reported to diminish [20,26]. In the remaining 5 infants the IVGTT could not be performed within those time limits. All infants were fasting except infant No. 10, who had been fed with 10 ml of a 5% glucose solution approximately 6 hours before the test. No mothers received any glucose solution during the delivery, but they were not fasted.

Glucose in a dose of 1.5 g per kg body weight in a 25—50 per cent solution was injected either via a scalp vein in 11 infants or through a catheter inserted in the umbilical artery in the other 11. There was no difference between the groups with regard to the route of glucose injection or the time required for the injection. The mean injection time was 7.8 min (range 3—14 min). Capillary blood samples to determine glucose were collected at 0, 10, 20, 30, 40, 50 and 60 min after the start of the injection.

c) **Insulin response at IVGTT.** In 9 IHR and 10 ILR an umbilical vein catheter was inserted at the IVGTT and introduced into the vena cava well above the hepatic veins. Venous blood samples, 1.5—3 ml, were drawn into heparinized test tubes at 0, 5, 10 and 20 min, centrifuged and stored for later insulin determinations.

1.3 Laboratory methods

Blood glucose was determined by a glucose oxidase method using a commercial preparation (KABI Reagens, Stockholm). Plasma glucose was determined using the same method adapted for microliter volumes [27]. Plasma insulin measurements were carried out at the Department of Endocrinology and Metabolism, Karolinska Hospital, using the double radioimmunoassay of HALES and RANDLE [14]. Urinary estriol was determined by a modification of BELING's technique [31] and HCS was measured using a commercial preparation (Phadebas®, PHARMACIA, Sweden) at the Hormone Laboratory, Karolinska Hospital.

1.4 Clinical neonatal score

The scoring system developed earlier [28] for evaluating infants of diabetic mothers (IDM), was adapted for application to these infants. The criteria chosen are listed in Tab. II, and they are more frequently recorded in IDM than in a population of infants of healthy mothers [8, 23].

Tab. II. Neonatal scoring system.

Scoring criteria	Degree	Points
1. Birth weight/ gestational age	<90th percentile	0
	≧90th percentile	1
2. "Diabetic fetopathy"	none	0
	moderate	1
	severe	2
3. Postnatal weight loss	<9 per cent	0
	9—11 per cent	1
	>11 per cent	2
4. Hyperexcitability	none	0
	moderate	1
	severe	2
5. Hypoglycemia	≧30 mg per 100 ml	0
	20—29 mg per 100 ml	1
	<20 mg per 100 ml	2
6. Hyperbilirubinemia	≦12.0 mg per 100 ml	0
	>12.0 mg per 100 ml	1
7. Congenital anomalies	none observed	0
	present	1
8. k-value	<1.4	0
	≧1.4	1
9. Immediate insulin response	<100 per cent of fasting value	0
	≧100 per cent of fasting value	1

For the birth weight/gestational age criterion the distribution curves for newborn Swedish infants computed by ENGSTRÖM and STERKY [10] was used. Criteria Nos. 3—7 were recorded using the notes in the hospital charts during the first 5 days as well as a personal examination of the infant at least once and usually twice by one of us. One or usually several blood glucose values were recorded for each infant and the lowest value recorded was used. Two criteria have been added to the ones originally used [28], namely a recorded high k-value at IVGTT (≧ 1.4 per cent) and a high immediate insulin response at the IVGTT (exceeding 100 per cent of fasting value at 5 min).

1.5 Statistical methods

The k-value at IVGTT was calculated according to the formula:

$$k_t = \frac{0.693 \times 100}{t\,\frac{1}{2}}$$

where $t\,\frac{1}{2}$ is the half-life time for blood glucose (in absolute values) during the first hour after the injection [15].

Comparisons of mean values for the groups were made by MANN-WHITNEY's ranking test. Analyses of changes within the groups were made by pairwise comparison. For methods and tables used, see SNEDECOR and COCHRAN [24].

2 Results

2.1 Mothers during pregnancy

The mean weight increase during pregnancy was 12.5 ± 2.7 and 11.3 ± 4.2 kg for high and low responders respectively ($p > 0.05$). There was no difference in urinary estriol excretion and no individual pathological decrease was seen. The HCS levels in plasma were also normal, in the 36th week mean values were 5.6 ± 0.8 and 6.1 ± 1.1 microgram/ml respectively ($p > 0.05$). The duration of labor was identical, 9.4 ± 6.6 hours in high and 9.3 ± 6.2 hours in low responders. No mothers had a k-value below 1.0 during or after pregnancy. For a more detailed description of changes in insulin response during pregnancy, see EDSTRÖM, CERASI and LUFT [9].

2.2 Infants

a) **Fetal and neonatal conditions.** Fetal bradycardia was recorded in two infants during labor (Nos. 27 and 29), fetal tachycardia and meconium-stained amniotic fluid in one (No. 24a), and meconium-stained amniotic fluid alone in another infant (No. 11).

The APGAR score was normal in all infants at birth, except two (Nos. 24a and 27a) who scored 6 points each. Minor disturbances were registered in the breathing performance of 5 infants (Nos. 10, 14, 23, 28 and 29) but they all disappeared within 40 minutes. No differences were seen in rectal temperature, pulse or respiratory rate between the IHR and ILR. The mean birth weight did not differ significantly between the two groups, but the postnatal weight loss was more pronounced in ILR ($p < 0.05$). The glucose level in peripheral blood decreased in a

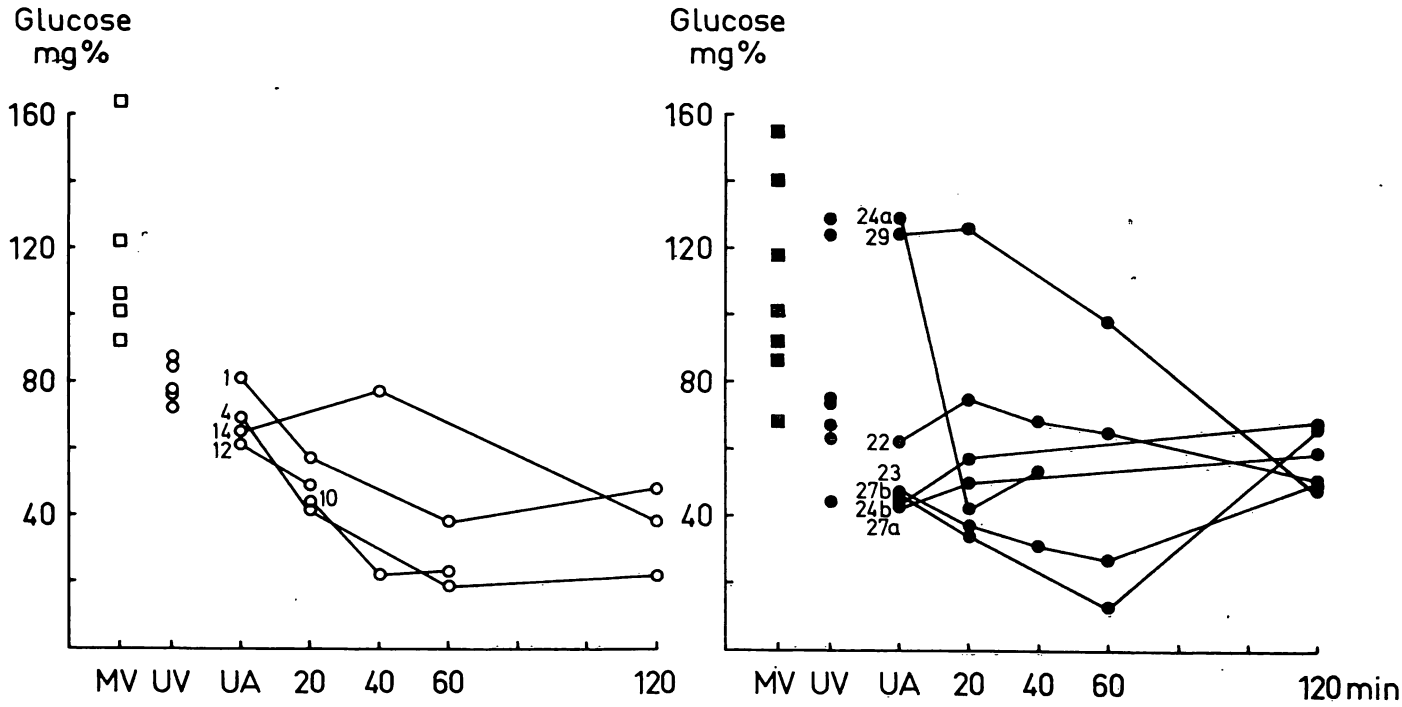


Fig. 1. Individual plasma glucose levels at delivery and during the following two hours in five IHR (open circles) and seven ILR (closed circles). The numbers in the graph refer to the infants' numbers in Tab. I. MV = maternal vein, UV = umbilical vein, UA = umbilical artery.

Tab. III. Mean values ± SD for plasma insulin and blood glucose at delivery (UV) and during IVGTT in infants of high insulin responders (IHR) and in infants of low insulin responders (ILR).

Parameter	Group		UV	0 min	5 min	10 min	20 min	30 min	40 min	50 min	60 min
Plasma insulin μU/ml	IHR	$\bar{x}$	20.8	24.7	43.1	53.6	83.7	—	—	—	—
		SD	10.8	17.8	40.1	66.5	90.3	—	—	—	—
		n	9	10	9	9	9				
	ILR	$\bar{x}$	20.3	24.3	56.3	59.2	89.9	—	—	—	—
		SD	12.4	18.9	33.2	43.0	75.9	—	—	—	—
		n	9	10	10	10	10				
Blood glucose mg/100 ml	IHR	$\bar{x}$	118.8	51.9	—	295.4	304.7	286.6	248.7	227.7	204.2
		SD	71.4	9.0	—	120.6	121.8	126.3	110.4	114.3	102.0
		n	9	9		9	9	9	9	9	9
	ILR	$\bar{x}$	122.0	50.6	—	346.8	343.6	318.0	273.2	253.4	209.9
		SD	70.4	17.1	—	105.0	87.9	74.9	64.2	66.1	71.1
		n	9	10		10	10	10	10	10	10

Tab. IV. Mean values ± SD for k-values and plasma insulin increase during IVGTT in infants of high responders (IHR) and low insulin responders (ILR). ΔI_{0-20} = total insulin increment during the first 20 min of IVGTT.

Group		k-value at IVGTT	Insulin increase during IVGTT, μU/ml plasma			ΔI_{0-20} μU/ml/20 min
			0—5 min	0—10 min	0—20 min	
IHR	$\bar{x}$	1.11	+17.2	+27.7	+57.8	582.5
	SD	0.45	24.2	56.2	78.5	949.0
	n	11	9	9	9	9
ILR	$\bar{x}$	1.40	+32.0*	+34.9**	+65.5**	746.3
	SD	0.64	35.7	43.3	79.1	710.0
	n	11	10	10	10	10

* Increase within the group is significant with $p < 0.025$
** Increase within the group is significant with $p < 0.05$

similar fashion in both groups during the first 2 hours after birth (Fig. 1).

The mean values of plasma insulin in UV and corresponding glucose values did not differ between IHR and ILR (Tab. III). Prior to the IVGTT the insulin values showed a non-significant increase of about 5 micro U per ml from the UV values and the glucose values decreased significantly ($p < 0.001$ in both groups).

b) **IVGTT.** The mean k-value for IHR was 1.11 + 0.45 and that for ILR 1.40 ± 0.64, the difference being non-significant (Tab. IV). Individual k-values are given in Tab. I. Five ILR and 2 IHR had a k-value above 1.4 (Fig. 2).

Mean plasma insulin and blood glucose levels during the IVGTT are given in Tab. III. The differences found between the groups are not significant. The mean increase of plasma insulin above the fasting level at 5 min after the glucose injection (the immediate insulin response) was 32.0 ± 35.7 micro U per ml for ILR and 17.2 ± 24.2 micro U per ml for IHR (Tab. IV), but again there was no significant difference between the groups. The same was true for the total insulin increment (ΔI_{0-20}). However, within the group of ILR the insulin increase at 5 min was significant at 2.5% level and later at 5% level while the response within the IHR was not significant.

The individual insulin responses, expressed as per cent increase above the fasting value, are shown in Fig. 3. Among the IHR only 1 infant out of 9 showed an increase in plasma insulin at 5 min that exceeded 100% of the fasting value; all the others had a response of less than 75%. This infant had the highest k-value in that group but a

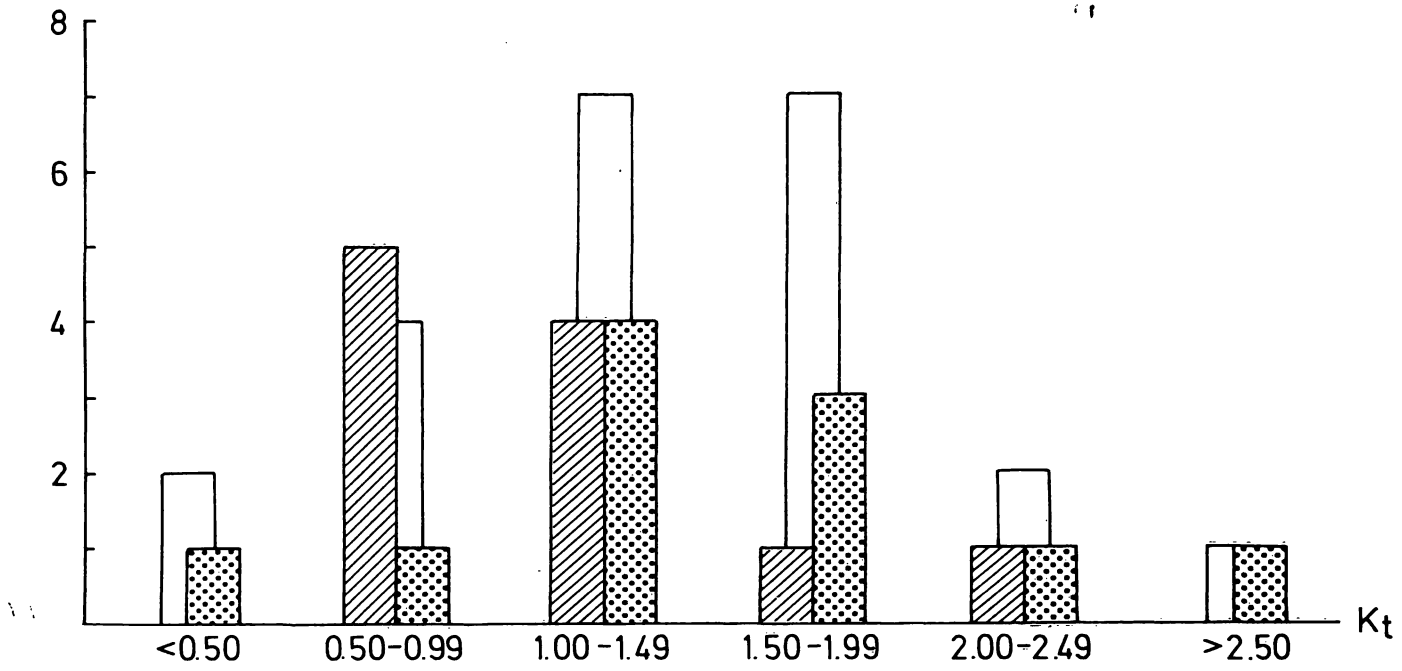


Fig. 2. Distribution of k-values (k_t). Striped bars denote k-values of IHR and dotted bars k-values of ILR. The unfilled bars in the back-ground denote k-values of 26 IDM in an earlier study by THALME and EDSTRÖM [30].

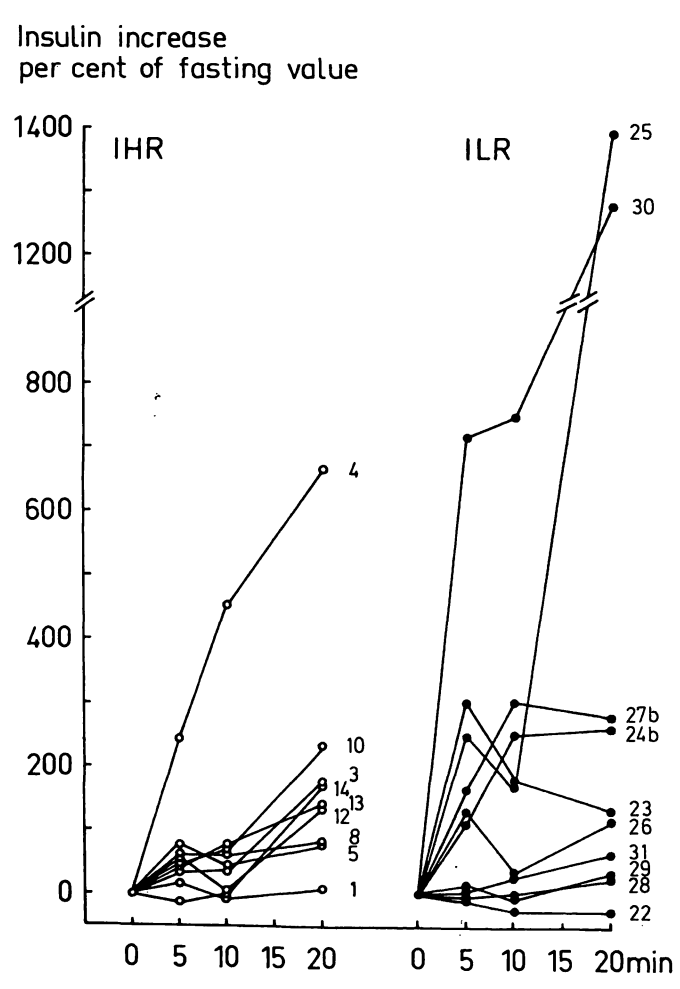
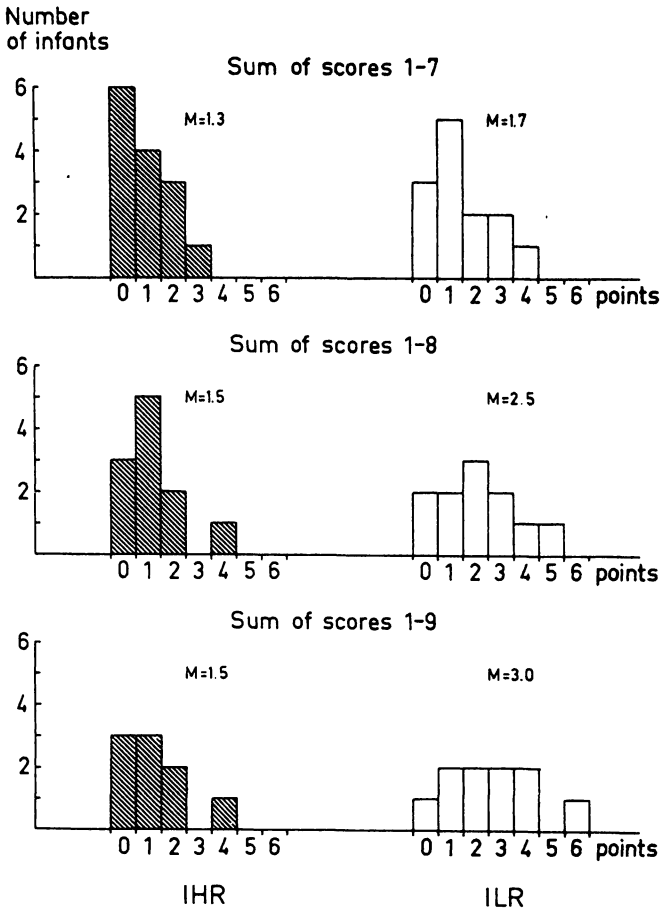


Fig. 3. Insulin increase during IVGTT, expressed as a percentage of fasting values in 9 IHR (open circles) and 10 ILR (closed circles).

glucose level of only 187 mg per 100 ml blood at 10 min after the start of the glucose injection. Among the ILR 6 infants out of 10 showed an insulin response of more than 100% at 5 min. There was no correlation between the infant's k-value and its birth weight ($r = 0.12$, $n = 22$), nor between their k-values and immediate insulin responses ($r = 0.02$, $n = 19$). Neither was there any correlation between their insulin responses and birth weight ($r = -0.10$, $n = 19$).

c) **Neonatal score.** The sum of scoring points was calculated for each infant, and the distribution of these individual sums within the groups is shown in Fig. 4. Since the k-value and the immediate insulin response could not be determined in all infants, three different scoring sums were calculated. The first includes the first seven scoring criteria (1—7), all of which were calculated for each infant studied. The second includes the first seven criteria + k-value (1—8) and the third the first seven criteria + k-value + immediate insulin response (1—9). The mean



sums of the first seven criteria were 0.9 ± 1.0 and 1.5 ± 1.3 for IHR and for ILR respectively ($p > 0.05$). When the k-value was added the mean sums for both groups increased and finally, when all 9 criteria were added together, the mean sum for ILR increased further so that a significant difference was obtained between the groups (IHR $= 1.3 \pm 1.6$ and ILR $= 2.6 \pm 1.8$, $p < 0.01$).

The frequency of each criterion in the two groups, expressed as a percentage of the maximal score possible for the whole group, is shown in Fig. 5. The criterion high birth weight/gestational age, which selects large-for-date infants, is the only criterion seen more often in the IHR. All other criteria were equally often or more frequently encountered in the ILR group, particularly the criteria hyperexcitability, hypoglycemia, high

Fig. 4. Distribution of the individual sums of scores for IHR and ILR. The top diagram includes all 27 infants with scores calculated for the first 7 criteria in Tab. II, the middle diagram includes 22 infants with 8 criteria and the bottom diagram 19 infants with all criteria. M = median value for the group.

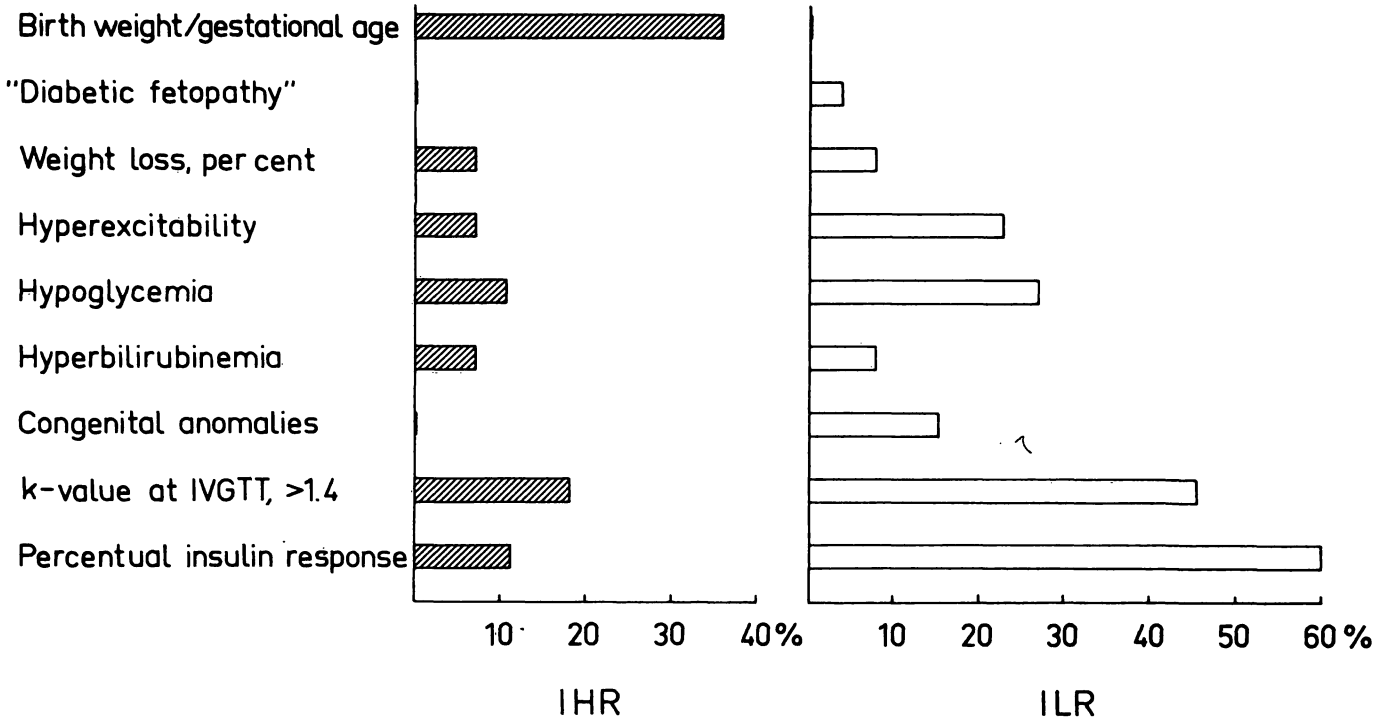


Fig. 5. The proportion of the total scoring sum for each criterion found in each group. The first criterion refers to the cases with a birth weight $\geqq$ 90th percentile (see Tab. II)

k-value and insulin response. The two latter are definitely the most frequent ones but no correlation was obtained between them. Eight out of 10 ILR showed either one or both of these criteria as compared to only 2 out of 9 IHR, and these distributions differ significantly ($p < 0.005$) when analyzed by the chi square test.

3 Discussion

Women who deliver large or malformed babies have been reported to run a higher risk than others of developing clinical or chemical diabetes mellitus later on [13, 17, 22]. However, these observations were not based on studies of the carbohydrate tolerance **during** pregnancy, and the occurrence of a transient gestational diabetes might have passed unnoticed. The latter condition is well known both to affect the infant's glucose tolerance [3, 11, 19] and to cause symptoms of diabetic fetopathia [23]. It is not known, though, whether the infant of a truly prediabetic woman might be affected in the same way during pregnancy.

The low insulin response to GIT in healthy subjects, which has been used here as the criterion for selecting the mothers, **is postulated to be typical of — even if not always identical with — a prediabetic state** [5]. Recently, CERASI and LUFT [6] through linear follow-up studies carried out over some years have shown that a large proportion of the low responders develop transient or permanent signs of carbohydrate intolerance. **None of the low responders studied here developed any signs of a pathological glucose tolerance during the pregnancy in question,** and consequently **any recorded "diabetogenic" effect on their infants might be considered related to the prediabetic stage.**

The mean k-value at IVGTT was somewhat but not significantly higher in the ILR than in the IHR. However, the mean value and the distribution of the k-values in the ILR group (Fig. 4) was almost identical to that previously reported by THALME and EDSTRÖM [28] for a group of IDM whose mothers were very rigidly controlled and had almost normal blood glucose levels in the last trimester. Thus, if the size of the groups is increased, we could expect to find a significant difference between the ILR and the IHR.

In the same way the immediate insulin response showed a somewhat higher mean value for ILR, although the difference was not significant. **No correlation was found between the k-values at IVGTT and the immediate insulin responses.** This is different from what has been reported for insulin and k-value in adults [16, 30] and in older children [25], suggesting that **the k-value in normal newborn infants is normally more influenced by factors other than the insulin response.** MÖLSTEDT-PEDERSEN and JÖRGENSEN [21] found a positive correlation between these two factors, but they measured the insulin at a later stage (12 min after the glucose injection) and their group also included 50 per cent of IDM.

A number of clinical indications and routine laboratory findings, known to appear in IDM during the first few days, were evaluated by a scoring system which has previously been applied to such infants [28] who scored a significantly higher sum than infants of healthy mothers. All the criteria except high birth weight for gestational age (or large-for-date infants) were somewhat more commonly registered in the ILR but the groups did not differ significantly, neither as to the mean sum nor the distribution of the score. When the criteria high k-value and high insulin response were added, the two groups of infants showed some difference. These two criteria — either one or both of them — were found in 9 out of 11 ILR and only in 2 out of 11 IHR, and added together they seem to be significantly related to the presence of a low insulin response to glucose in the mother.

The normal human fetal pancreas has been shown to respond poorly to glucose both in vitro [18] and in vivo [29] despite the fact that its capacity for synthesizing insulin seems to be normal [7, 12]. In newborn infants of healthy mothers this poor response persists at least for the first few days of life while IDM show a marked and prompt insulin release after the same glucose stimulus [3, 21]. This has been related to the exposure of the fetus in a diabetic pregnancy to a sustained hyperglycemia [23], but recently ASPLUND [1] has shown that also a minor and

intermittent maternal hyperglycemia during the latter part of pregnancy can increase the sensitivity of the fetal pancreas to glucose. The mothers mentioned here all had normal glucose tolerance and normal fasting glucose levels, but the k-values at IVGTT in late pregnancy were slightly lower in the low responders and consequently their postprandial blood glucose levels might have been repeatedly higher than those of the high responders.

The tendencies here described in the infants, namely a higher glucose tolerance and a more pronounced initial insulin response to glucose in ILR, should at present not be interpreted as being more than tendencies. The k-value at IVGTT in the newborn infant is also influenced by factors other than the insulin secretion from the pancreas. It is also subject to a wide normal variation and the sample should be enlarged in order to see whether the groups really do differ in k-value. If this can be confirmed it could be of considerable clinical value. **The presence of a high k-value and/or an increased initial insulin response during an IVGTT in the neonate would then be an important clue for the detection of a prediabetic state in the mother. It seems that this might be an even earlier indication from the infant of a disturbed carbohydrate metabolism in the mother than for instance a high birth weight.**

Summary

Diabetic mothers affect their offspring during pregnancy, sometimes giving rise to the complete symptoms of diabetic fetopathia with the typical appearance of the child high birth weight, hyperinsulinism, etc. Some of these traits have also been reported to appear in the infants some time before the onset of diabetes in the mother, but no prospective study of infants born to truly prediabetic mothers has yet been reported. Thus it is not possible to say whether or not the previously reported effects are related to an undetected, subclinical diabetes in the mother.

A prospective study of the insulin response to glucose during pregnancy [9] has been previously published, which included 11 women with a low insulin response to glucose infusion (GIT) — a prediabetic type of insulin response according to the definition of CERASI and LUFT [5] — and a control group of 14 women with a high insulin response to glucose infusion. In the following the neonatal findings in these 13 infants of low insulin responders (ILR) and 14 infants of high responders (IHR) are reported.

During pregnancy all the mothers maintained a normal glucose tolerance as determined by intravenous glucose tolerance tests (IVGTT) and they had normal blood levels of HCS and a normal excretion of estriol in urine.

Blood samples for determination of glucose and insulin in blood were collected from the infants at birth, during the first two hours and at an IVGTT carried out on 22 infants at 4—24 hours of age. The glucose tolerance test was performed by injecting 1.5 g glucose per kg body weight. In 19 infants plasma insulin was determined during the IVGTT. At birth and during the first week all infants were evaluated clinically to determine whether any of the criteria 1—7 seen in Tab. II were present. Each infant received a sum of scores ranging from 0 to a theoretical maximum of 11. For the majority of infants it was possible to evaluate the k-value at IVGTT and to classify the immediate insulin response into high or low (Tab. II), making the maximum score sum 13.

Blood glucose was determined using a glucose oxidase method, and plasma insulin using a radioimmunoassay technique.

The immediate insulin response was defined as the increase above fasting value of insulin at 5 min after the start of the injection. A lower limit of 100% above the fasting value was arbitrarily chosen for a high insulin response. Also arbitrarily, a lower limit of 1.4 was set for what was considered a high k-value at IVGTT.

The birth weight was slightly but not significantly higher among the IHR, but the weight loss during the first days was more pronounced in the ILR.

The umbilical levels of insulin and glucose and corresponding fasting levels at IVGTT (Tab. III) did not differ between the groups. Insulin did not change significantly before the IVGTT, while glucose decreased rapidly and uniformly during the first two hours (Fig. 1).

The k-value tended to be higher in the ILR, 1.40 ± 0.64 as compared to 1.11 ± 0.45 in IHR. This difference, however, was not quite significant. The plasma insulin increased significantly during the first 20 min in ILR, while in the IHR the response was lower and the increase not significant (Tab. IV). The difference in response between the groups was not significant. There was no correlation between the birth weight, k-value or insulin response. The scoring sum for the seven clinical criteria was higher in the ILR, but the difference between the groups was not significant until the criteria 8 and 9 were added **(Fig. 3)**.

The findings reported above indicate that the infants of low insulin responders — which would include the prediabetic individuals — might be affected during their fetal life in a way similar to infants of diabetic

mothers, at least concerning their glucose tolerance and ability to respond rapidly to a glucose stimulus by an increase in insulin output. This finding could be an important clue for the detection of a prediabetic state in the mother — probably more important than a high birth weight.

Keywords: Glucose infusion, Glucose tolerance, Infants, Insulin response, Newborn, Prediabetics.

Zusammenfassung

Untersuchungen über Neugeborene von Müttern mit hoher und niedriger Insulinausschüttung nach Glucoseinfusion. Glucosetoleranz, Insulinausschüttung und klinisches Verhalten während der frühen Neonatalperiode.

Diabetische Mütter beeinflussen ihre Nachkommenschaft während der Schwangerschaft, wobei manchmal das voll entwickelte Bild der diabetischen Foetopathie mit dem typischen Erscheinungsbild beim Neugeborenen, hohes Geburtsgewicht, Hyperinsulinismus usw. entsteht. Es ist bekannt, daß einige dieser Merkmale schon vor dem Auftreten des mütterlichen Diabetes beim Kind beobachtet werden, es ist jedoch noch keine prospektive Studie an Kindern von tatsächlich prädiabetischen Müttern durchgeführt und mitgeteilt worden. Daher ist es auch nicht möglich, zu entscheiden, ob die zuvor angesprochenen Veränderungen auf einen unentdeckten, subklinischen Diabetes mellitus der Mutter zurückgeführt werden können oder nicht.

Kürzlich wurde eine prospektive Untersuchung über die Insulinausschüttung nach Glucoseapplikation während der Schwangerschaft [9] publiziert, in der 11 Frauen mit niedriger Insulinsekretion nach Glucoseinfusion — entsprechend der Definition von Cerasi und Luft [5] ein für Prädiabetes typisches Verhalten des Inselorganes — und eine Kontrollgruppe von 14 Frauen mit hoher Insulinsekretionsrate nach Infusion berücksichtigt wurde. Im folgenden werden die Befunde jener 13 Neugeborener, deren Mütter eine niedrige Insulinsekretionsrate (ILR) zeigten und jener 14 Neugeborener mit hohen mütterlichen Sekretionsraten (IHR) mitgeteilt.

Alle Mütter hatten aufgrund intravenöser Glucosetoleranztests konstant normale Zuckertoleranzwerte während der Schwangerschaft, normale HCS-Spiegel im Blut und die Östrogenausscheidung im Urin lag ebenfalls im Normbereich. Von den Neugeborenen wurden zum Zeitpunkt der Geburt, während der ersten 2 Lebensstunden und bei 22 Neugeborenen 4—24 Stunden nach der Geburt im Rahmen eines intravenösen Glucosetoleranztestes Blutproben zur Bestimmung von Glucose und Insulin abgenommen. Beim Glucosetoleranztest wurden 1,5 g Glucose/kg Körpergewicht i. v. verabfolgt. Bei 19 Kindern konnte während des intravenösen Glucosetoleranztestes das Plasmainsulin bestimmt werden. Bei der Geburt und während der ersten Wochen wurden alle Kinder klinisch im Hinblick auf das Vorkommen irgend eines der in **Tab. II** angegebenen Kriterien untersucht. Jedes Neugeborene erhielt eine Notensumme, die zwischen 0 und dem theoretischen Maximum 11 lag. In der Mehrzahl der Fälle konnte eine Bewertung der k-Werte beim i. v. Glucosetoleranztest und eine Einstufung der Frühreaktion des Inselorganes in hohe oder tiefe Sekretionsraten vorgenommen werden **(Tab. II)**, was die höchste Bewertungssumme auf 13 ansteigen ließ. Der Blutzucker wurde mit einer Glucoseoxidasemethode und das Plasmainsulin mit einer Radioimmunoassay-Technik bestimmt. Als „Sofortreaktion des Inselorganes" wurde jener Insulinspiegelanstieg 5 min nach Beginn der Infusion definiert, der über den Hungerwert hinausging. Als starke Reaktion des Inselorganes wurde willkürlich der Insulinspiegel, welcher 100% über dem Insulin-Hungerwert lag, gewählt. Desgleichen wurde für die Definition eines hohen k-Wertes beim i. v. Glucosetoleranztest eine untere Grenze von 1,4 willkürlich vorgegeben.

Bei den Kindern mit starker Reaktion des Inselorganes lagen die Geburtsgewichte geringfügig aber nicht signifikant höher, wohingegen der Gewichtsverlust während der ersten Lebenstage in der Gruppe mit schwacher Reaktion des Inselorganes deutlicher ausgeprägt war. Die Insulin- und Glucosespiegel im Nebelschnurblut sowie die Hungerspiegel dieser Parameter beim i. v. Glucosetoleranztest **(Tab. III)** unterschieden sich nicht in den beiden Stichproben. Der Insulinspiegel veränderte sich nicht signifikant vor Beginn des i. v. Glucosetoleranztestes, wohingegen die Glucosekonzentration schnell und einheitlich während der beiden ersten Lebensstunden abnahm **(Fig. 1)**. Die k-Werte lagen in der Gruppe mit schwacher Reaktion der Langhans-Zellen mit $1{,}40 \pm 0{,}64$ eher höher im Vergleich zu $1{,}11 \pm 0{,}45$ in der Gruppe mit starker Reaktion. Diese Differenz war jedoch nicht mehr signifikant. In der Gruppe mit schwacher Reaktion stiegen die Plasmainsulinwerte signifikant. In der Gruppe mit schwacher Reaktion stiegen die Plasmainsulinwerte signifikant während der ersten 20 Infusionsminuten an, während in der Gruppe mit starker Antwort des Inselorganes der Anstieg nicht signifikant und verzögert war **(Tab. IV)**. Die Unterschiede in den Reaktionsmustern der beiden Gruppen waren nicht signifikant. Es fanden sich keine Korrelationen zwischen dem Geburtsgewicht, den k-Werten oder der Insulinausschüttung. Die Bewertungssumme für die 7 klinischen Kriterien war in der Gruppe mit schwacher Reaktion höher; der Unterschied zwischen den beiden Gruppen war jedoch erst signifikant, wenn die Kriterien 8 und 9 einbezogen wurden (Fig. 3).

Die mitgeteilten Beobachtungen weisen darauf hin, daß **Kinder von Müttern mit schwacher Reaktion des Inselorganes — zu welchen die prädiabetische Schwangere zählt — während ihres intrauterinen Lebens in ähnlicher Weise beeinflußt werden wie Kinder von diabetischen Müttern; dies gilt zumindest hinsichtlich**

ihrer Glucosetoleranz und ihrer Fähigkeit, auf einen Glucosestimulus mit einer raschen Steigerung der Insulinsekretion zu antworten. Dieser Befund könnte ein wichtiger Hinweis bei der Suche nach dem mütterlichen Prädiabetes sein und ist vermutlich ein weit wichtigerer Indikator als das zu hohe Geburtsgewicht.

Schlüsselwörter: Glucoseinfusion, Glucosetoleranz, Insulinausschüttung, Neugeborene, Prädiabetes, Kinder.

Résumé

Les enfants nés de mères présentant une forte réponse insulinique et ceux nés de mères présentant une faible réponse insulinique à une perfusion de glucose. Tolérance au glucose, réponse insulinique et aspect clinique au cours dela période néonatale précoce

Les mères diabétiques lèsent leurs enfants au cours de la grossesse, parfois en donnant une image complète de foetopathie diabétique: aspect typique de l'enfant, gros poids de naissance, hyperinsulinisme. Certains de ces symptômes ont été rapportés, parfois, chez des enfants nés de mères dont le diabète n'était pas encore apparent. Toutefois, il n'existe pas à l'heure actuelle d'étude prospective portant sur des enfants nés de mères présentant un véritable prédiabète. Dès lors, il est impossible de dire si les effets déjà cités sont à mettre en correlation avec un diabète maternal, subclinique et non diagnostiqué, ou pas.

Une étude prospective de la réponse insulinique à la perfusion de glucose pendant la grossesse [9] a déjà été publiée. Celle-ci comprenait 11 patientes présentant une réponse insulinique faible à la perfusion de glucose (GIT), (ce qui correspond à une réponse insulinique de type prédiabétique, selon la définition de CERASI et LUFT [5]), elle comprenait outre, 14 femmes présentant une forte réponse insulinique et utilisées comme groupe témoin. Nous allons rapporter ici les découvertes néonatales observées respectivement chez 13 enfants de mères à réponse faible (IHR) et chez 14 enfants de mères à réponse forte.

Au cours de la grossesse, toutes les mères conservèrent une tolérance normale au glucose, ce qui fut mis en évidence par l'hyperglycémie provoquée par injection intraveineuse (IVGTT), leur taux de HCS plasmatique demeura normal ainsi que leur oestriolurie.

On pratiqua des mesures de la glycémie et de l'insulinémie du nouveauné, à la naissance et au cours des deux premières heures de la vie. On pratiqua une hyperglycémie provoquée par voie intraveineuse chez 22 nouveau-nés à respectivement, 4 et 24 heures de vie. L'hyperglycémie provoquée fut réalisée par l'injection de 1,5 g de glucose par kilo de poids. Chez 18 enfants, le taux d'insuline plasmatique fut déterminé en même temps. A la naissance et durant la première semaine de vie tous les enfants furent soumis à des examens cliniques visant à étudier la présence des critères 1—7 rapportés dans le **Tab. II.** Chaque enfant reçu une quotation de 0 à 11, qui est le maximum théorique. Chez la majorité des enfants, une quotation de la valeur de K au cours de l'hyperglycémie put être réalisée, traduisant une réponse insulinique immédiate forte ou faible, ce qui porta le score maximum à 13.

La glycémie fut mesurée en utilisant une méthode à la glucose oxydase. L'insulinémie fut évaluée par une technique radio-immunologique.

La réponse insulinique immédiate se définit comme suit: augmentation de l'insulinémie au delà de la valeur à jeun, 5 minutes après le début de l'injection de sucre. La limite inférieure de la réponse insulinique forte fut fixée de façon arbitraire à 100% de la valeur de l'insulinémie à jeun. C'est aussi de façon arbitraire que nous avons fixé à 1,4 la limite inférieure des valeurs de K élevées lors de l'hyperglycémie provoquée.

Le poids de naissance fut augmenté de façon nette mais non significative chez les enfants nés de femmes IHR; tandis que la perte de poids au cours des premiers jours du postpartum fut plus importante chez les enfants nés de mères ILR.

Les valeurs d'insulinémie et de glycémie ombilicales, et ces mêmes valeurs à jeun, mesurées au cours des hyperglycémies provoquées **(Tab. III)** ne varièrent pas d'un groupe à l'autre. L'insulinémie ne se modifia pas de façon signifiacative avant l'hyperglycémie intraveineuse, tandis que la glycémie chuta rapidement et uniformément pendant les premières deux heures **(Fig. 1)**.

La valeur de K avait tendance à être élevée chez les ILR: $(1{,}40 \pm 0{,}64)$ en comparaison avec les IHR: $(1{,}11 \pm 0{,}45)$. Cependant, cette différence ne fut pas significative. L'insulinémie plasmatique augmenta de façon significative durant les 20 premières minutes, chez les ILR, tandis que chez les IHR, la réponse fut plus faible, et l'augmentation non significative **(Tab. IV)**. La différence de réponse entre les groupes ne fut pas significative. Il n'y eut pas de corrélation entre le poids de naissance, la valeur de K, et la réponse insulinique. Le total des différents critères cliniques fut plus élevé chez les ILR, toutefois, la différence entre les groupes ne fut pas significative tant qu'on n'y ajouta pas les critères 8 et 9 **(Fig. 3)**.

Les faits rapportés ci-dessus montrent que **les enfants issus de mères ayant une réponse insulinique faible** (ce groupe correspondrait aux patientes prédiabétiques) **pourraient être atteints durant leur vie intra-utérine de la même façon que les enfants nés de mères diabétiques surtout en ce qui concerne leur tolérance au sucre et leur capacité de répondre rapidement à une augmentation de leur glycémie par une sécrétion accrue d'insuline. Ce fait pourrait constituer un indice important pour le dépistage du prédiabète maternel et de valeur très supérieure au poids de naissance élevé.**

Mots-clés: Enfants, nouveau-né, perfusion de glucose, prédiabète, réponse insulinique, tolérance au glucose.

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